REMARKS

Claims 30-74, 79, 80, 82, and 92, have been canceled without prejudice or disclaimer as being drawn to a non-elected invention. Claims 79 and 80 have been included in this group based on the action of September 25, 2007. Applicant reserves the right to pursue this claimed subject matter in one or more continuing applications.

Claims 1-29, 75-78, 81, 83-91, and 93-105 remain in the application. New claims 106-111 have been added. Claims 106-109 are focused on the therapeutic dose being administerable in one minute and begin contained in a single 10 ml vial. Both of these features are supported in the specification on page 21, and, as noted in the concurrently filed declaration of Dr. Brandom these traits provide significant clinical benefit. Claims 110 and 111 are drawn to the concentration of the medicament being 50 mg/ml, as is specifically referenced on page 38 of the application.

Claims 2, 4, 15-17, 27-29, 75-77, and 81 have been withdrawn from consideration based on the applicant's election. As will be noted below, each of these claims depends from an allowable base claim, and the undersigned requests rejoinder of these claims on allowance of the base generic claims.

The claims under consideration include claims 1, 3, 5-14, 18-26, 83-91, and 93-105. Common to each of these claims is the concept of a safe for injection, low volume formulation of dantrolene. Independent claim 1 describes a "safe for injection, low volume formulation of dantrolene or salts or analogues thereof". Independent claim 23 describes a dry powder formulation of dantrolene "which, upon addition of a liquid carrier, produces a safe for injection, low volume formulation". Independent claim 83 describes a composition comprising dantrolene or a salt of dantrolene where the particulate size is less than 2μm and where the composition "is safe for injection, or is reconstitutable with liquid to be safe for injection". Independent claim 93 describes "a safe for injection, low volume formulation of dantrolene or salts or analogues thereof". Each of independent claims 103 and 104 describe methods of preparing "a safe for injection, low volume formulation of dantrolene or salts or analogues thereof".

Claims 1, 3, 5-8, 10-12, 22 and 95 have been rejected as being anticipated by JP 5320413. This rejection is traversed.

Attached to this amendment is an English language translation of JP5320413. As will be noted on page 3, at line 15, JP5320413 describes a formulation "for ordinary oral administration" (emphasis added). Thus, JP5320413 is not an injectable formulation as required by the claims. An oral formulation does not serve the same function of an injectable formulation as noted in the declaration of Dr. Brandom at items 10 and 25. Furthermore, in the same paragraph on page 3 of the English language translation, a number of excipients listed in the JP5320413 formulation are not safe for injection, including without limitation hydroxypropyl cellulose (which is not approved for any injectable route at any level), food coloring, and aromas. Further, Embodiment 5 on page 4 of the translation discusses the use of "granules" which are understood in the art to have a size ranging from 4 mesh (nominal sieve opening 2.0 mm, that is, 2,000 microns) to 10 mesh (4.76 mm, that is, 4,760 microns) see Pharmaceutics and Compounding Laboratory, School of Pharmacy, University of North Carolina at Chapel Hill, www.pharmalab.unc.edu/powders/text.htm. This not only falls outside the scope of the claimed invention, but would probably be lethal on injection. From the articles referenced in Dr. Brandom's declaration at items 7 and 24, it is clear that particulate size is important as large particles of dantrolene sodium can kill mammals on i.v. injection. The articles referenced in item 7 are based on the claimed invention, while the article referenced in item 24 represents a failure by others to achieve the invention. JP 5320413, being unrelated to an injectable formulation, wholly ignores issues relating to particle size. Attached hereto is a passage from Injectable Dispersed Systems: Formulation, Processing and Performance by Diane J. Burgess, ed. Informa Healthcare, 1, edition (May 23, 2005, ISBN-10 0849336996, at page 79, which indicates " Particle size distribution is one of the most important characteristics of injectable dispersed systems...The intravenous injection of emulsion droplets above 5 microns is clinically unacceptable because they cause the formation of pulmonary emboli. The size requirement for suspension administered intravenously is even smaller since unlike emulsion droplets solid particles lack flexibility that would enable passage through small capillaries." In addition, tonicity of the injectate should be

considered, while there is no equivalent in oral administration. The tonicity of four of the five embodiments of JP 5320413 is extremely high, at values known to cause thrombosis on intravenous injection. Thus, as JP 5320413 is directed to an oral formulation, essential technological hurdles necessary for injectable pharmaceuticals are ignored in JP 5320413 with the consequence that embodiments of the specified ingredients, while possibly suitable for oral formulations, are patentably unacceptable for injection. In view of this, the rejection of claims 1, 3, 5-8, 10-12, 22 and 95 under 35 U.S.C. 102 should be withdrawn.

Claims 1, 3, 5-14, 18-26, 83-91, and 93-105 have been rejected as being obvious over U.S. Patent 4,543,359 to Ellis, U.S. Patent 6,294,192 to Patel, U.S. Patent 6,495,164 to Ramstack, U.S. Patent 5,510,118 to Bosch, and JP 5320413. This rejection is traversed.

As discussed in detail in the concurrently filed declaration of Dr. Barbara Brandom, there has been a long felt but unsatisfied need for the claimed invention (see items, 7, 8, 11, 12, 16, 17 (particularly see the attached abstract referred to therein), 22, and 23). Furthermore, the declaration of Dr. Barbara Brandom establishes that where the applicants have succeeded (see item 7 and the attached references), others have previously tried and failed (see item 24 and the attached reference). None of the references identified by the Examiner show or suggest a safe for injection, low volume formulation of dantrolene as set forth in the claims (a detailed discussion of the references is set forth below). No combination of the references would make the claimed invention obvious to one of ordinary skill in the art. If it were obvious, the claimed invention would have been made long ago, as there has been acute need for the invention as established in the declaration of Dr. Barbara Brandom. In short, the independent claims recite specific features which are not obvious to one of ordinary skill in the art. Claims 1 and 23 require that the dantrolene is present in a concentration wherein 3 to150 milliliters of liquid carrier provides approximately 500 milligrams of medicament. No reference sets forth these specific requirements for a low volume delivery of dantrolene, and no combination of the references sets forth these specific requirements. Claim 83 requires the dantrolene be present in a particulate form of less than 2 microns in size, and that it be present with a water soluble surfactant.

Claim 83 has been amended to include the limitation of claim 93 that less than 5 milliliters of liquid carrier provides approximately 500 milligrams of medicament. As noted above, the particle size is very important in terms of avoiding death to an animal in which dantrolene is injected. Many of the references fail to address particle size at all as they are not directed to injectable formulations. Furthermore, many of the references fail to discuss stabilization of the formulation or the need for agents such as surfactants. All of the references fail discuss a formulation of dantrolene wherein less than 5 milliliters of liquid carrier provides approximately 500 milligrams of medicament, and no combination of the references set forth these specific requirements. Claims 103 and 104 discuss methods of preparing safe for injection dantrolene formulations wherein the dantrolene is dissolved or dispersed in 3 to 150 milliliters of a liquid carrier. As noted above in connection with claims 1 and 23, no combination of references shows or makes obvious these formulation requirements. Moreover, the declaration of Dr. Barbara Brandom details how prior art injectable dantrolene formulations are prepared, and their drawbacks, and establishes that the quick preparation methods with the low volume formulations characterized by claims 103 and 104 make a substantial improvement to the state of the art (see items 11-23).

As discussed above, the references cited do not show or suggest a safe for injection, low volume formulation of dantrolene as set forth in the claims. Ellis discloses a method of using dantrolene sodium for treatment of cardiac arrhythmias. No mention is made of formulation limitations, methods or challenges. Two formulations were administered. The first, administered to mice, was self-made using an excipient which is not approved for injection (Methocel) and injected intraperitoneally., not intravenously, and the second, which was administered to dogs intravenously, was the currently marketed solution. Neither was high concentration, low volume, nor did Ellis include any discussion about the need or benefits of high concentration, low volume dantrolene sodium. The concentration of both was 0.5 mg/ml, that of the currently marketed injectable product, and an order of magnitude less than the lower end of the range concentration claimed in the instant invention. The patent to Patel identifies well known challenges to formulating hydrophobic drugs and discusses the limitations and drawbacks of three approaches—micelles, emulsions and micro-emulsions,

for certain uses and drugs. Patel focuses on their common use of "triglycerides". Patel then discloses a different formulation technology comprising a combination of certain hydrophobic and hydrophilic surfactants for use in oral formulations for oral administration. No mention of dantrolene is made in his list of hundreds of compounds. None of the formulation technologies identified, either in the art or the described technology, are embodied in the instant application. The claims of Patel are limited to oral administration, and the document contains no information applicable to intravenous administration. Patel contains no discussion of the need, benefit or use of low volume, high concentrated formulations of dantrolene, or prompt availability requirements. Patel requires the combination of hydrophilic and hydrophobic surfactants in combination, whereas the instant invention uses only hydrophilic surfactants. Hence, at best, Patel is an example of various formulation technologies, and is unrelated to the problems addressed by the claimed invention and does not exhibit the functions or features of the claimed invention. Ramstack describes formulations for subcutaneous (SC) and intramuscular (IM) injections, comprising very large "microspheres", and methods to assure the viscosity of formulations with such large particles. The microspheres are defined as particles that contain an active agent or other agent dispersed or dissolved within a polymer that serves as a matrix or binder of the particle, and "range in size up to about 250 microns". The claims in Ramstack require the microspheres to exceed 10 microns in size. Thus, they are unacceptable and potentially lethal for intravenous injection. Because of the focus of Ramstack, it ignores the critical issues of intravenous administration. Ramstack requires either microparticles comprising a polymeric binder, an illustrative list of which includes excipients not approved for intravenous injection, or mixing the suspension of microparticles with a viscosity enhancing agent, again illustrated by a list of excipients which include items not approved for intravenous injection. Thus, there is no indication that this technology is intended for or could be used for or modified for intravenous injection. Ramstack has no mention of dantrolene whatsoever. Thus, there is no mention of the need or benefits of a high concentration, low volume dantrolene formulation. The patent to Bosch, unlike Patel and Ramstack, is directed to a method of producing injectable formulations, not oral formulations. One of ordinary skill in the art

would not look to references such as Patel and Ramstack which are specific to enhancing oral formulation, when making an injectable formulation. Furthermore, Bosch is directed to a process technology where milling operations are performed in a microfluidizer in conjunction with a surface modifier (see claim 1). Dantrolene is not among the myriad of drugs referenced in Bosch. Thus, there is no mention of the need or benefits of a high concentration, low volume dantrolene formulation. In short, the four references collectively do not disclose technology sufficient to successfully prepare a high concentration, low volume dose of dantrolene sodium safe for intravenous administration, nor can hindsight (although improper) be used to do so, as the references collectively lack any showing of a need for, the benefits of, a suggestion of, or an embodiment of a high concentration, low volume dantrolene formulation. Contrary to the claimed invention, the formulations described in some of the references would be lethal if administered by intravenous injection. None of the patents discuss the need or benefit of low volume high concentration formulation for any drug, let alone dantrolene. None discuss the need for and benefits of immediate pharmacokinetic activity of a drug when administered for any drug per se, let alone dantrolene in particular.

In view of the above, claims 1-29, 75-78, 81, 83-91, and 93-111 should now be in condition for allowance. Reconsideration and allowance of the claims at an early date is requested.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

A provisional petition is hereby made for any extension of time necessary for the continued pendency during the life of this application. Please charge any fees for such provisional petition and any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,

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(54) Title of the Invention
Stable dantrolene sodium preparation

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Specification

1. Title of Invention: Stable dantrolene sodium preparation

2. What is claimed is:

(1) A stable dantrolene sodium preparation wherein 1, or 2 or more salts selected from the group comprising normal and hydrogen alkali metal salts are mixed within a 1 – { [5 – (p-Nitrophenyl) furfurylidene] amino} hydantoin sodium hydrate (hereinafter referred to as "dantrolene sodium") in suspension so that the pH of the solution is 9-11.

(2) A stable dantrolene sodium preparation according to claim 1 in the form of a dry syrup or suspension.

3. Detailed Description of the Invention

The present invention concerns a stable dantrolene sodium preparation combined with 1, or 2 or more salts selected from the group comprising normal and hydrogen alkali metal salts.

Dantrolene sodium is a durable skeletal muscle relaxant having a hydantoin ring, it is an extremely useful drug for counteracting skeletal muscle twitching etc. caused by diseases of the central nervous system and spinal cord.

However, when dantrolene sodium is suspended in water it quickly becomes unstable and the hydantoin ring shown in the formula below, which is subject to rapid hydrolysis, opens. This activity is therefore a weak point.

[formula]

Dantrolene sodium

Therefore, as a result of the inventors' varied research into preventing the breakdown of dantrolene sodium, they discovered the present invention wherein 1, or 2 or more salts selected from the group comprising normal and hydrogen alkali metal salts are added to dantrolene sodium to prevent the breakdown of dantrolene sodium within a solution.

The normal alkali metal salts used in the present invention are those that are pharmaceutically permissible, for example sodium citrate, sodium succinate, potassium tartrate, sodium malate, sodium chloride, potassium chloride etc. The hydrogen alkali metal salts used in the present invention may be, for example, sodium bicarbonate, disodium hydrogen phosphate, dipotassium hydrogen phosphate.

The proportion in which the dantrolene sodium and alkali metal salts are mixed together in the preparation of the present invention is as follows: in 1 ml of solution, 1-50 mg, but preferably 2-30 mg alkali metal salts per 1-50 mg of dantrolene sodium, to a pH of 9-11. The preparation of the present invention can be made up as a liquid

suspension, and for oral administration as a liquid preparation it may be made into a powder or granule syrup (meaning a ready-to-use syrup suspension).

The following is an embodiment showing the stable effect of the present invention.

Embodiment: A brown syrup bottle was filled with each of the following suspensions, and after being stored at 40°C for 7 days, the remaining dantrolene sodium was separated by thin layer chromatography for analysis and measured by photo absorption method.

	Formulation	Amount (mg/ml)	pH at time of formulation	Remaining rate (%)
A	Dantrolene sodium	5.0	10.2	70.4
B	Dantrolene sodium Sodium citrate	5.0 8.5	9.6	98.2
C	Dantrolene sodium Potassium tartrate	5.0 11.3	10.0	92.4
D	Dantrolene sodium Sodium succinate	5.0 8.1	9.6	99.7
E	Dantrolene sodium Sodium chloride	5.0 5.8	9.3	98.4

As clearly shown by these results, the present invention sufficiently prevents the hydrolysis of dantrolene sodium.

Furthermore, as the present invention is for ordinary oral administration, sweeteners such as sucrose, mannitol and sorbitol, suspenders such as sodium carboxymethyl cellulose and methyl cellulose, binders such as hydroxypropyl cellulose and polyvinylpyrrolidone, preservatives such as methylparaben and propylparaben, food colourings and other colouring agents, aromas, and surfactants such as polyoxyethylene stearate (polyoxyl (40) stearate) and polyoxyethylene sorbitan monooleate (polysorbate 80) can be added.

Embodiment 1

25 g sucrose, 850 mg sodium citrate and 200 mg methylparaben were dissolved in purified water, 500 mg of dantrolene sodium was suspended within the solution and purified water added to a total volume of 100 ml.

Embodiment 2

25 g sucrose, 1.13 g potassium tartrate and 200 mg methylparaben were dissolved in purified water, 500 mg of dantrolene sodium was suspended within the solution and purified water added to a total volume of 100ml.

Embodiment 3

25g sucrose, 810 mg sodium succinate, 200 mg methylparaben and 1g sodium carboxymethyl cellulose were dissolved in purified water, 500 mg of dantrolene

sodium was suspended within the solution and purified water added to a total volume of 100 ml.

Embodiment 4

25 g sucrose, 580 mg sodium chloride and 200 mg methylparaben were dissolved in purified water, 500 mg of dantrolene sodium was suspended within the solution and purified water added to a total volume of 100ml.

Embodiment 5

500 mg of dantrolene sodium, 850 mg sodium citrate, 200 mg methylparaben and 23.3 g powdered sugar were combined in a preparation and 150 mg hydroxypropyl cellulose added to form granules. 100 ml of water was added to this granule preparation.

Kouichi Sasaki, Patent Attorney

2. PARTICLE SIZE MEASUREMENT

Particle size distribution is one of the most important characteristics of injectable dispersed systems. For example, sedimentation or creaming tendencies of a dispersed system can be minimized by changing the particle size of the system. The stability of injectable dispersed systems can also be conveniently monitored by measuring changes in particle size and size distribution. The biofate of some dispersed system dosage forms is dependent on their particle size distribution (3,4). Tomazic-Jezic et al. (5) reported an intensive phagocytosis of small- and medium-sized polystyrene particles (1.2 and 5.2 μm) after peritoneal injection of the polystyrene particles into mice but no engulfment of large polystyrene particles (12.5 μm) by the macrophages was observed. The intravenous injection of emulsion droplets above 5 μm is clinically unacceptable because they cause the formation of pulmonary emboli (6,7). The size requirement for suspensions administered intravenously is even smaller since unlike emulsion droplets solid particles lack flexibility that would enable passage through small capillaries.

A wide range of particle sizes is typical of dispersed systems as evidenced by intravenous fat emulsions that contain droplets in the range of 10 nm–1 μm and by emulsions used as contrast media in computerized tomography that are of 1–5 μm size (8,9). Droplets larger than 5 μm are sometimes present because of inefficient homogenization or as a result of emulsion instability. Clearly, it is difficult to use a single method for determination of all particle sizes in such a wide range. For most colloidal dispersions the mean particle size as well as size distribution can be accurately determined by photon correlation spectroscopy (PCS). However, this method is not capable of measuring sizes greater than 3 μm in diameter. Laser diffraction can be used for measurement of particles greater than 3 μm and is therefore useful for detecting larger particles. Photomicroscopy can also be used for sizing large particles. Table 1 shows various particle size analysis methods and approximate size ranges for each. Some of these methods including microscopy, electrical/optical sensing zone, and light scattering are reviewed in detail.